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Method for producing
indole derivatives on a solid phase

5 The invention relates to a method for producing indole
derivatives on a solid phase, where the attachment to
the solid phase takes place on the indole nitrogen
through transacetalization of dialkoxymethyl-protected
indoles with a solid phase which has vicinal diol
10 groups and, after synthetic chemistry on the solid
phase, the functionalized indole derivative is cleaved
"without trace" off the solid phase.

15 Solid-phase synthesis is now an established method in
the pharmaceutical industry, on the one hand for
producing compound libraries for the purpose of
combinatorial synthesis, and on the other hand in the
highly automated parallel synthesis of individual
substances. These result in compounds which have good
structural diversity and can be subjected to mass
20 screening in test systems. The finding of active
substance lead structures and protection agents or
drugs can be considerably shortened by this procedure.
In the solid-phase synthesis of chemical compounds, the
molecules to be assembled are bound via a linker to a
25 polymeric support during the synthesis.

30 In connection with these solid-phase syntheses there is
a need for strategies for synthesizing indole
derivatives because the indole nucleus has proved to be
an important key structure in a large number of
bioactive compounds (ref.: Gribble, g.W. in Comprehen-
sive Heterocyclic Chemistry II, Katritzky, A.R.; Rees,
C.W., Scriven, E.F.V. Eds., Pergamon, 1996, Vol.2).
Solid-phase methods of particular interest are those in
35 which no functional group (functionality) of the solid
phase remains on the product, i.e. the elimination from
the solid phase takes place "without trace".

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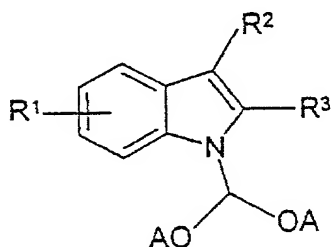
Smith et al. were the first to use the indole nitrogen as point of attachment to the solid phase (ref.: Smith, A.L., et al., Tetrahedron Lett. 1998, 39, 8317). Reaction of a free indole with Ellmann's THP resin (ref. Ellmann, J.A. et al., Tetrahedron Lett. 1994, 35, 9333-9336) forms an aминаl linkage between 3,4-dihydro-2H-pyran and the indole nitrogen, which is cleaved again to give the free indole on addition of 10% trifluoroacetic acid.

The invention was based on the object of providing a novel, simple method for producing indole derivatives on a solid phase which utilizes the principle of elimination "without trace".

This object is achieved by the method of the invention.

The invention relates to a method for producing indole derivatives on a solid phase, where the attachment to the solid phase takes place on the indole nitrogen through transacetalization of dialkoxymethyl-protected indoles with a solid phase which has vicinal diol groups and, after synthesis chemistry on the solid phase, the functionalized indole derivative is cleaved "without trace" off the solid phase.

The invention further relates to a method for producing indole derivatives on a solid phase, where the attachment to the solid phase having vicinal diol groups takes place by transacetalization of dialkoxymethyl-protected indoles of the formula I



in which

R^1 is H, A, Hal, OA, CF_3 , CN, NA_2 or NO_2 ,

R^2 is H, A, $-(CH_2)_o$ -Hal, OA, CF_3 , OCF_3 , CN, NO_2 , COOA or NA_2 ,

5 R^3 is H, A, $-(CH_2)_o$ -Hal, OA, CF_3 , OCF_3 , CN, NA_2 , NO_2 or $SnBu_3$,

A is alkyl having 1 to 6 C atoms,

Bu is butyl,

o is 0, 1, 2 or 3

10 with the condition that at least one substituent R^1 , R^2 or R^3 is not H.

15 The definitions of all the radicals which occur more than once, such as, for example, A, are independent of one another.

Unless expressly indicated otherwise, the definitions of the radicals and parameters R^1 , R^2 , R^3 , R^4 , A, Y, m and n, and

20

(P)

hereinbefore and hereinafter are those indicated for formulae I to VII.

25

In the formulae hereinbelow and hereinafter, A is alkyl, is linear or branched, and has 1 to 6, preferably 1, 2, 3, 4, 5 or 6, C atoms. A is preferably methyl, ethyl, isopropyl, n-propyl, n-butyl, sec-butyl
30 or tert-butyl, also n-pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl or n-hexyl. A is particularly preferably methyl or ethyl.

35

$-(CH_2)_o$ -Hal is F, Cl, Br, I, fluoromethyl, chloromethyl, bromomethyl, iodomethyl, fluoroethyl, chloroethyl, bromoethyl, iodoethyl, fluoropropyl, chloropropyl, bromopropyl or iodopropyl. In particular, $-(CH_2)_o$ -Hal is chloromethyl.

Hal is preferably F, Cl, Br or I, particularly preferably chlorine.

5 R^1 is H, A, Hal, OA, CF_3 , OCF_3 , CN, NA_2 or NO_2 , where A has one of the meanings indicated above. R^1 may be in position 4, 5, 6 or 7 of the indole framework and, in particular, R^1 is in the 5 or 6 position. R^1 is particularly preferably H, CN or NO_2 . R^1 is very particularly preferably H, 5-CN, 6-CN or 5- NO_2 .

10 R^2 is H, A, $-(CH_2)_o$ -Hal, OA, CF_3 , OCF_3 , CN, NO_2 , COOH, COOA or NA_2 , where A and $-(CH_2)_o$ -Hal have one of the meanings indicated above. R^2 is preferably H or COOA. The subsequent synthetic chemistry on the solid phase
15 preferably takes place in the 3 position of the indole framework, i.e. on R^2 , or in the 2 position of the indole framework, i.e. on R^3 .

After the synthetic chemistry has taken place, therefore, R^2 is likewise $-(CH_2)_n$ - NH_2 , $-(CH_2)_n$ -NHA, -
20 $(CH_2)_n$ - NA_2 , Het or $-(CH_2)_n$ -Het-Ar. Particularly preferred for R^2 after synthetic chemistry has taken place is - $(CH_2)_n$ - NA_2 or $-(CH_2)_n$ -Het-Ar, where A has one of the meanings indicated above, n is 0, 1 or 2, and $-(CH_2)_n$ -Het-Ar has one of the preferred or very
25 preferred meanings mentioned hereinafter. n is particularly preferably 1.

R^3 is H, A, $-(CH_2)_o$ -Hal, OA, CF_3 , OCF_3 , CN, NA_2 , NO_2 or $SnBu_3$, where A and Hal have one of the meanings
30 indicated above, and o can be 0, 1, 2 or 3. Particularly preferred for R^3 is H, chloromethyl or $SnBu_3$.

After the synthetic chemistry has taken place, R^3 is
35 likewise Ar, particularly preferably CN-substituted phenyl, Het or $-(CH_2)_n$ -Het-Ar, particularly preferably 3,4-dichlorophenylpiperazin-4-ylmethyl, phenylpiperazin-4-ylmethyl or 2-chlorophenylpiperazin-4-ylmethyl. Ar is phenyl which is unsubstituted or

substituted one, two or three times by A, CN, OH, OA or Hal. Ar is therefore preferably phenyl, 2-, 3- or 4-methylphenyl, 2-, 3- or 4-ethylphenyl, 2-, 3- or 4-isopropylphenyl, 2-, 3- or 4-propylphenyl, 2-, 3- or 4-tert-butylphenyl, 2-, 3- or 4-cyanophenyl, 2-, 3- or 4-hydroxyphenyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-ethoxyphenyl, 2-, 3- or 4-isopropoxyphenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-chlorophenyl or 2-, 3- or 4-bromophenyl.

10

Het is a mononuclear or binuclear saturated, unsaturated or aromatic heterocycle which has 1 to 4 N, O and/or S atoms and may be unsubstituted or substituted one, two or three times by Hal, A, OH, OA, CF₃, CN or NO₂.

15

Het is preferably substituted or unsubstituted 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-pyrrolyl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, also preferably 1,2,3-triazol-4- or -5-yl, 1,2,4-triazol-4- or -5-yl, 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 2-, 3-, 4-, 5-, 6- or 7-1H-indolyl, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl, 1-, 2-, 3- or 4-carbazolyl, 1-, 2-, 3-, 4- or 9-acridinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl. The heterocyclic radicals may also be partially or completely

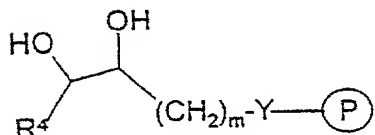
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hydrogenated. It may thus also be 2,3-dihydro-2-, -3-,
 -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl,
 tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetra-
 hydro-2- or -3-thienyl, 2,3-dihydro-2-, -3-, -4- or -5-
 5 pyrrolyl, 2,5-dihydro-2-, -3-, -4- or -5-pyrrolyl, 2-
 or 3-pyrrolidinyl, tetrahydro-2- or -3-pyrrolyl,
 tetrahydro-2- or -4-imidazolyl, 2,3-dihydro-2-, -3-,
 -4-, -5-, -6- or -7-1H-indolyl, 2,3-dihydro-3-, -4- or
 -5-pyrazolyl, tetrahydro-3- or -4-pyrazolyl, 1,4-di-
 10 hydro-2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-2-, -3-,
 -4-, -5- or -6-pyridyl, 1,2,3,6-tetrahydro-2-, -3-,
 -4-, -5- or -6-pyridyl, 2-, 3- or 4-piperidinyl, 1-,
 2-, 3- or 4-azepanyl, 2-, 3- or 4-morpholinyl,
 tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-
 15 dioxan-2-, -4- or -5-yl, hexahydro-3- or -4-
 pyridazinyl, hexahydro-2-, -4- or -5-pyrimidinyl, 2-,
 3- or 4-piperazinyl, 1,2,3,4-tetrahydro-2-, -3-, -4-,
 -5-, -6-, -7- or -8-quinolinyl, 1,2,3,4-tetrahydro-1-,
 -3-, -4-, -5-, -6-, -7- or -8-isoquinolinyl. Het is
 20 particularly preferably piperazin-4-yl.

Het, Ar and n in $-(CH_2)_n$ -Het-Ar have one of the
 preferred or particularly preferred meanings indicated
 above. $-(CH_2)_n$ -Het in $-(CH_2)_n$ -Het-Ar is preferably
 25 piperazin-4-ylmethyl, piperazin-4-ylethyl, piperidin-4-
 ylmethyl or piperidin-4-ylethyl and Ar in $-(CH_2)_n$ -Het-Ar
 is a phenyl which is unsubstituted or mono-, di- or
 trisubstituted by A, CN, OH, OA or Hal. $-(CH_2)_n$ -Het-Ar
 is very particularly preferably (3,4-dichlorophenyl)-
 30 piperazin-4-ylmethyl, phenylpiperazin-4-ylmethyl and
 (2-chlorophenyl)piperazin-4-ylmethyl.

Suitable solid phases having vicinal diol groups are,
 for example, solid phases of the formula II



II

in which

(P) is a solid phase without terminal functional group,

R⁴ is H or A,

5 A is alkyl having 1 to 6 C atoms,

m is 1, 2, 3 or 4 and

Y is O, S, NH or NA.

10 R⁴ is H or A, where A has one of the meanings indicated above. R⁴ is particularly preferably H.

Y is O, S, NH or NA, where A has one of the meanings indicated above. Y is particularly preferably O.

15 m is 1, 2, 3 or 4, particularly preferably 1.

o is 0, 1, 2 or 3, particularly preferably 1 or 2, very particularly preferably 1.

20 The symbol (P) represents the polymeric support material and all atoms of the anchor group of a solid phase apart from the terminal functional group. The anchor groups of a solid phase, also called linkers, are necessary for the
25 attachment of the compound which is to be functionalized to the solid phase. A summary of syntheses on a solid phase and the solid phases and/or linkers which can be employed for this purpose is given, for example, in Novabiochem - The Combinatorial Chemistry Catalog,
30 March 99, pages S1-S72.

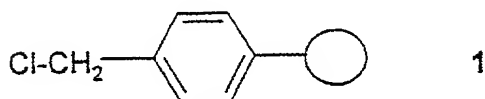
For the Merrifield resin, which is referred to chemically as chloromethylpolystyrene-divinylbenzene and whose polymeric support material is
35 copolystyrene/1% divinylbenzene, the symbol

(P)

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represents chloromethylpolystyrene-divinylbenzene without the functional chlorine group.

Merrifield resin (ref. Novabiochem - The Combinatorial Chemistry Catalog, March 99, p. 10) can likewise be depicted in a chemical formula 1



where

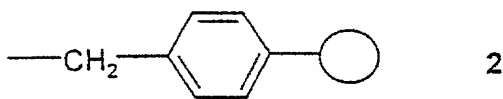
\pm is a polymeric support material

and the polymeric support material is copolystyrene/1% divinylbenzene.

The symbol



and thus the term "represents the polymeric support material and all atoms of the anchor group of a solid phase apart from the terminal functional group" or the term "a solid phase without terminal group" means, for example for the Merrifield resin of formula 1, the substituents of the formula 2



where

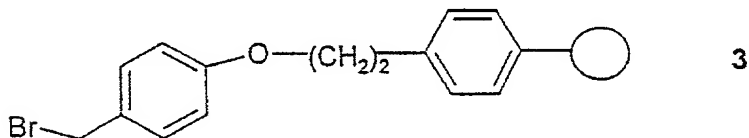
\pm is a polymeric support material

and the polymeric support material is copolystyrene/1% divinylbenzene.

The symbol



and thus the term "represents the polymeric support material and all atoms of the anchor group of a solid phase apart from the terminal functional group" or the term "a solid phase without terminal group" means, for example for the 4-(bromomethyl)phenoxyethyl polystyrene of formula 3, (ref. Novabiochem - The Combinatorial Chemistry Catalog, March 99, p. 8)



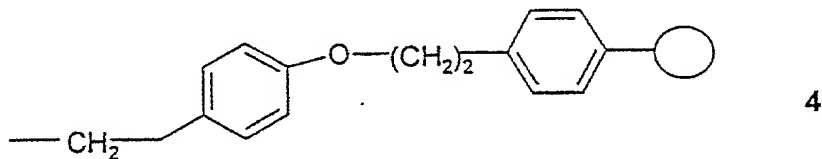
10

where

± is a polymeric support material

15 and the polymeric support material is copolystyrene/1% divinylbenzene,

the substituents of the formula 4



20

where

± is a polymeric support material

25

and the polymeric support material is copolystyrene/1% divinylbenzene.

30 Polymeric support materials of the solid phase are selected in particular from the group of crosslinked polystyrenes, crosslinked polyacrylamides or other resins, natural polymers or silica gels.

The group of crosslinked polystyrenes, crosslinked polyacrylamides or other resins includes polyacrylamide, polymethacrylamide, poly(hydroxyethyl methacrylate), polyamide, polystyrene, polystyrene/polyethylene glycol graft copolymers, (meth)acrylate copolymers of, for example, (meth)acrylic acid, (meth)acrylic esters and/or itaconic acid, crotonic acid, maleic acid or polyurethane foams, epoxy resins or other copolymers.

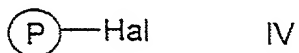
The group of natural polymers includes agarose, cellulose, alginate, chitosan, dextran, levan, xanthan, collagen, X-carrageenan, agar, pectin, ramanian, wood chips, microcrystalline cellulose, hexosamine or gelatin.

The group of silica gels includes all industrially produced as well as natural silica xerogels (silica gels for short), such as kieselguhr or diatomaceous earth.

The particle size of the solid phase based on polymeric support materials is preferably used in the range from 1 μm to 500 μm . The particles may be homogeneous or heterogeneous in their size distribution, and homogeneous particle sizes are preferred.

Solid phases having vicinal diol groups can in some cases be purchased (ref. Novabiochem - The Combinatorial Chemistry Catalog, March 99), but they can also be produced in analogy to Leznoff, C.C. and Wong, J.Y., Can. J. Chem. 1973, 51, 3756 by the following method in which

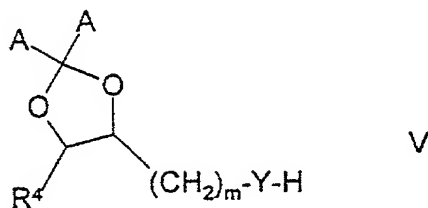
(a) a solid phase of the formula IV



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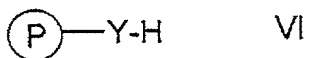
in which

(P) is a solid phase without terminal functional group,
and Hal is Cl or Br, is reacted with a compound of the formula V



in which A, R⁴, Y and m have one of the meanings indicated in formula II, or

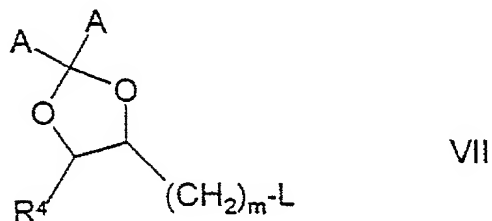
(b) a solid phase of the formula VI



in which

(P) is a solid phase without terminal functional group,

and Y has a meaning indicated in formula II, is reacted with a compound of the formula VII



in which A, R⁴ and m have a meaning indicated in formula II, and L is Cl, Br or a free, reactively functional modified OH group.

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Examples of suitable compounds of the formula IV are Merrifield resin (chloromethylpolystyrene-divinylbenzene), brominated PPOA resin, brominated Wang resin, bromo-(4-methoxyphenyl)methyl polystyrene, 4-(bromo-
5 methyl)phenoxyethyl polystyrene, 4-(bromomethyl)-phenoxyethyl polystyrene (Wang Br), 4-bromo polystyrene, 4-methyltrityl chloride resin, 4-methoxytrityl chloride resin, NovaSyn® TG bromo resin, NovaSyn®
10 dichlorotrityl alcohol TG resin, bromoacetamidomethyl NovaGel™, (bromomethyl)phenylacetamidomethyl NovaGel™, (4-bromophenyl)diisopropylsilyloxymethyl polystyrene or 2-bromo-1-ethoxyethane-1-oxy NovaSyn® (ref. Novabiochem - The Combinatorial Chemistry Catalog, March 99, pp. 7-15, 17, 56 and 58).

15 A particularly preferred compound of the formula V is 2,2-dimethyl-1,3-dioxolane-4-methanol.

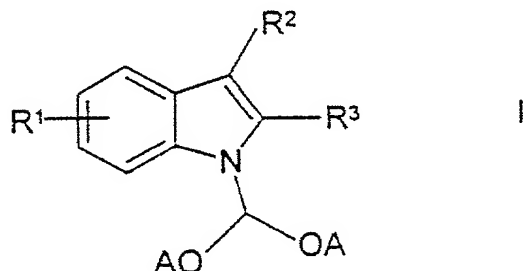
Suitable phases of the formula VI where Y is O is, for example, the Wang resin (ref.: Novabiochem - The Combinatorial Chemistry Catalog, March 99, pp. 30-42) or hydroxymethylpolystyrene. Suitable phases of the
20 formula VI where Y is NH are, for example, N-(2-aminoethyl)aminomethyl polystyrene, aminomethylated polystyrene, amino-(4-methoxyphenyl)methyl polystyrene, N-benzylaminomethyl polystyrene, MBHA resin (4-methylbenzhydrylamine resin), N-methylaminomethyl
25 polystyrene, NovaSyn® TG amino resin, aminomethyl NovaGel™, NovaSyn® TGR resin, Rink Amid NovaGel™, 4-sulfamylbenzoyl NovaSyn® TG resin, 4-sulfamylbenzoyl NovaGel™, amino PEGA resin or Rink amide PEGA resin (ref.: Novabiochem - The Combinatorial Chemistry Catalog, March 99, pp. 1, 2, 18-20, 23 and 25-30).

30 Fmoc-protected supports, for example Rink Amide resin, Sieber Amide resin or Weinreb AM resin (ref.: Novabiochem - The Combinatorial Chemistry Catalog, March 99, pp. 21-24) are likewise suitable because an amino group is liberated by elimination of the Fmoc protective group (fluoren-9-ylmethoxycarbonyl = Fmoc).

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Reactively functionally modified OH groups are, for example, tosylates or mesylates. The OH groups are converted into a leaving group, which make nucleophilic substitution possible.

Dialkoxymethyl-protected indoles of the formula I



in which R^1 , R^2 , R^3 and A have the meanings indicated in Claim 2, are preferably produced by reacting the free indoles substituted by R^1 , R^2 or R^3 with the appropriate orthoformate. Reaction with triethyl orthoformate is particularly suitable, in which case diethoxymethyl-protective indoles are produced.

The substituent $SnBu_3$ is introduced by regioselective lithiation in position 2 of the dialkoxymethyl-protected indole derivative, i.e. $R^3 = H$ is intermediate for $R^3 = Li$, and subsequent reaction with tri-n-butyltin chloride.

The transacetalization, i.e. the reaction of the dialkoxymethyl-protected indole derivatives with solid phases having vicinal diols, takes place under slightly acidic conditions, the solid phase-bound indole derivative forming a cyclic acetal.

The transacetalization usually takes place in an inert solvent in the presence of a catalytic amount of an acid, for example p-toluenesulfonic acid, camphorsulfonic acid, hydrochloric acid or else in the

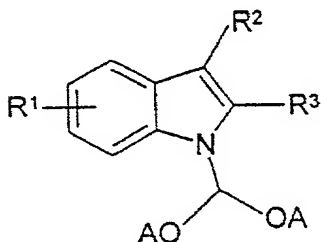
presence of an acid ion exchanger, in particular of a catalytic amount of p-toluenesulfonic acid.

The reaction time depends on the conditions used and is between a few minutes and several days, and the reaction temperature is between about 0° and 150°C, normally between 20° and 100°C, preferably between 20° and 40°.

Suitable inert solvents are, for example, hydrocarbons such as benzene, toluene or xylene; chlorinated hydrocarbons such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or 1,4-dioxane; ethylene glycol dimethyl ether (diglyme); ketones such as acetone or butanone; amides such as acetamide, N-methyl-pyrrolidone (NMP), dimethylacetamide or dimethylformamide (DMF); nitriles such as acetonitrile; sulfoxides such as dimethyl sulfoxide (DMSO); carbon disulfide; nitro compounds such as nitromethane or nitrobenzene or mixtures of the solvents mentioned.

1,4-Dioxane is particularly suitable for the transacetalization.

Transacetalization of dialkoxymethyl-protected indole derivatives of the formula I



in which

R¹ is H, A, Hal, OA, CF₃, OCF₃, CN, NA₂ or NO₂,

R² is H, A, -(CH₂)₆-Hal, OA, CF₃, OCF₃, CN, NO₂, COOA or NA₂,

R^3 is H, A, $-(CH_2)_o$ -Hal, OA, CF_3 , OCF_3 , CN, NA_2 , NO_2 or $SnBu_3$,

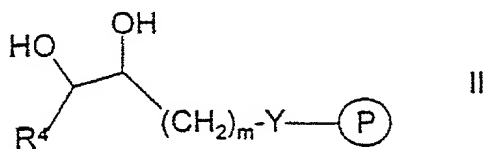
A is alkyl having 1 to 6 C atoms,

Bu is butyl,

5 o is 0, 1, 2 or 3

with the condition that at least one substituent R^1 , R^2 or R^3 is not H,

with a solid phase having vicinal diol groups, of the formula II



in which

15 (P) is a solid phase without terminal functional group,

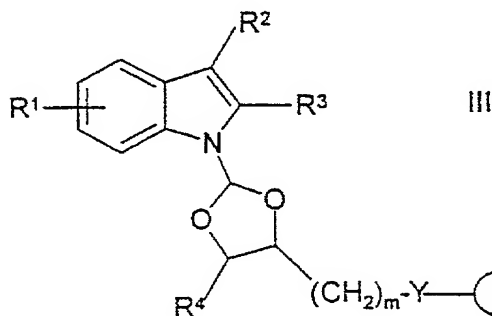
R^4 is H or A,

A is alkyl having 1 to 6 C atoms,

m is 1, 2, 3 or 4 and

Y is O, S, NH or NA,

20 results initially in indoles, which are bound to the solid phase, of the formula III



25 in which

(P) is a solid phase without terminal functional group,

R^1 is H, A, Hal, OA, CF_3 , OCF_3 , CN, NA_2 or NO_2 ,

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R^2 is H, A, $-(CH_2)_o-Hal$, OA, CF_3 , OCF_3 , CN, NO_2 , COOA or NA_2 ,

R^3 is H, A, $-(CH_2)_o-Hal$, OA, CF_3 , OCF_3 , CN, NA_2 , NO_2 or $SnBu_3$,

5 R^4 is H or A,

A is alkyl having 1 to 6 C atoms,

Bu is butyl,

n is 0, 1 or 2,

m is 1, 2, 3 or 4,

10 o is 0, 1, 2 or 3 and

Y is O, S, NH or NA,

with the condition that at least one substituent R^1 , R^2 or R^3 is not H, which are further functionalized by the subsequent synthetic chemistry.

15 After the synthetic chemistry has taken place, the substitution pattern for the compounds of the formula III changes in such a way that additionally

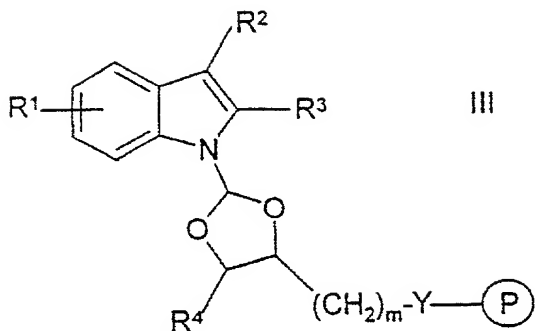
R^2 can be $-(CH_2)_n-NH_2$, $-(CH_2)_n-NHA$, $-(CH_2)_n-NA_2$, Het or $-(CH_2)_n-Het-Ar$ and

20 R^3 can be Ar, Het or $-(CH_2)_n-Het-Ar$, where

Ar is phenyl which is unsubstituted or substituted one, two or three times by A, CN, OH, OA or Hal, and

25 Het is a mono- or binuclear saturated or unsaturated or aromatic heterocycle which has 1 to 4 N, O and/or S atoms and which may be unsubstituted or substituted one, two or three times by Hal, A, OH, OA, CF_3 , CN or NO_2 .

30 The invention likewise relates to the solid phase-bound indole derivatives of the formula III



in which

(P) is a solid phase without terminal functional group,

R¹ is H, A, Hal, OA, CF₃, OCF₃, CN, NA₂ or NO₂,

R² is H, A, -(CH₂)_o-Hal, OA, CF₃, OCF₃, CN, NO₂, COOA or NA₂,

R³ is H, A, -(CH₂)_o-Hal, OA, CF₃, OCF₃, CN, NA₂, NO₂ Ar, Het, -(CH₂)_n-Het-Ar or SnBu₃,

R⁴ is H or A,

A is alkyl having 1 to 6 C atoms,

Ar is phenyl which is unsubstituted or substituted one, two or three times by A, CN, OH, OA or Hal,

Het is a mono- or binuclear saturated, unsaturated or aromatic heterocycle which has 1 to 4 N, O and/or S atoms and which may be unsubstituted or substituted one, two or three times by Hal, A, OH, OA, CF₃, CN or NO₂,

Bu is butyl,

n is 0, 1 or 2,

m is 1, 2, 3 or 4,

o is 0, 1, 2 or 3 and

Y is O, S, NH or NA,

with the condition that at least one substituent R¹, R² or R³ is not H.

IR spectroscopy is a suitable analytical method for detecting the solid phase-bound indole derivatives of the formula III as long as the substituents R¹, R², R³ and/or R⁴ are IR-active and generate a specific signal.

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The loading of the solid phase is usually between 0.3 and 1.5 mmol/g, in particular between 0.3 and 0.8 mmol/g.

5 Reactions suitable for the subsequent synthetic chemistry are all those which have also been described for syntheses in solution for functionalizing indole derivatives and which are known to the skilled worker, but the reaction conditions must not lead to acetal
10 cleavage and thus to elimination from the solid phase. Particularly suitable reactions are those which functionalize the indole precursors in the 2 or 3 position. Suitable examples are nucleophilic substitutions, in particular the Mannich reaction, oxidations, reductions, Pd-catalyzed aryl couplings,
15 for example by the Suzuki or Negishi method or the Stille coupling, especially the Stille coupling, iodolysis of a stannane and subsequent Pd-catalyzed coupling by the method of Heck or Sonogashira or Pd-catalysed formylations.
20

In order to avoid acidic conditions in the Mannich reaction, in this case the compounds of the formula III with $R^2 = H$ are preferably reacted with a
25 chloroalkyldialkylamine preferably in DMF. The solid phase-bound indole derivatives of the invention are, however, likewise stable under the reaction conditions of glacial acetic acid/dichloromethane in the ratio 1:4 to 4:1 for Mannich reactions. In particular, a glacial
30 acetic acid/dichloromethane ratio of 1:4, 1:1 and 4:1 is suitable, and glacial acetic acid/dichloromethane is very particularly preferably used in the ratio 4:1. A compound of the formula III with R^3 equal to H is likewise preferably reacted in glacial acetic acid/
35 dichloromethane (4:1) with formaldehyde and an arylpiperazine, where aryl in arylpiperazine may be phenyl which is unsubstituted or substituted once or twice by A, CN, OH, OA or Hal, in particular a phenyl

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which is unsubstituted or substituted once or twice by Hal.

The Mannich reaction is an example of the synthetic chemistry at the 3 position of the indole framework, but this nucleophilic substitution is not restricted to the 3 position of the indole framework.

An example of the synthetic chemistry at the 2 position of the indole framework is the Stille coupling. This entails compounds of the formula III with $R^3 = \text{SnBu}_3$ being reacted with an aryl bromide or iodide with palladium catalysis. The catalyst combination $[\text{Pd}_2(\text{dba})_3]/\text{tert-Bu}_3\text{P}/\text{CsF}$ is particularly suitable (ref.: Littke, A.F. and Fu, g.C. Angew. Chem. Int. Ed. 1999, 38, 2411; $\text{Pd}_2(\text{dba})_3 = \text{tris}(\text{dibenzylideneacetone})\text{-dipalladium}$). The Stille coupling is likewise not restricted to the 2 position of the indole framework.

A further example of the synthetic chemistry at the 2 position of the indole framework is a classical nucleophilic substitution in which a compound of the formula III with $R^3 = -(\text{CH}_2)_o\text{-Hal}$, where o and Hal have a preferred or particularly preferred meaning, is reacted with a secondary amine, in particular an arylpiperazine, where aryl in arylpiperazine may be a phenyl which is unsubstituted or substituted once or twice by A, CN, OH, OA or Hal, in particular a phenyl which is unsubstituted or substituted once or twice by Hal. The reaction takes place in an inert solvent, in particular in DMF. The reaction time depends on the conditions used and is between a few minutes and several days, and the reaction temperature is between about 0° and 150°C , normally between 20° and 100°C , preferably between 20° and 40° .

35

The method of the invention is suitable in particular for synthesizing solid phase-bound indole derivatives of the formula III in which at least one of the radicals mentioned has one of the preferred meanings

indicated above. Some preferred groups of solid phase-bound indole compounds can be expressed by the following part-formulae IIIa to IIIf which correspond to formula III and in which the unspecified radicals have the meaning indicated for formula III but in which

in IIIa R^1 is H, CN or NO_2 ,
 R^2 is H or COOA,
 R^3 is H, $-(CH_2)_o$ -Hal or $SnBu_3$,
10 R^4 is H,
 m is 1,
 o is 1 and
 Y is O,

with the condition that at least one substituent R^1 , R^2 or R^3 is not H;

in IIIb R^1 is H, CN or NO_2 ,
 R^2 is H, $-(CH_2)_o$ -Hal, COOA, $-(CH_2)_n$ - NA_2 or $-(CH_2)_n$ -Het-Ar,
20 R^3 is H, $SnBu_3$, Ar or $-(CH_2)_n$ -Het-Ar,
 R^4 is H,
 m is 1,
 n is 1
 o is 1, and
25 Y is O;

with the condition that at least one substituent R^1 , R^2 or R^3 is not H;

in IIIc R^1 is H or CN,
30 R^2 is COOA, $-(CH_2)_n$ - NA_2 or $-(CH_2)_n$ -Het-Ar,
 R^3 is H or Ar,
 R^4 is H,
 m is 1,
 n is 1 and
35 Y is O;

in IIId R^1 is CN,
 R^2 is H,
 R^3 is $-(CH_2)_n$ -Het-Ar,

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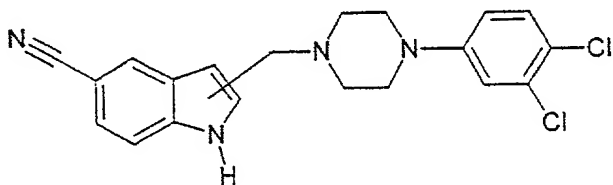
R⁴ is H,
m is 1,
n is 1 and
Y is O;

5

in IIIe R¹ is H or CN,
R² is COOA, -(CH₂)_n-NA₂ or arylpiperazin-4-ylmethyl,
R³ is H or Ar,
10 R⁴ is H,
m is 1,
n is 1
Y is O and
aryl in arylpiperazin-4-ylmethyl is phenyl
15 which is unsubstituted or substituted
once or twice by A, CN, OH, OA or Hal;

in IIIf R¹ is CN,
R² is H,
20 R³ is arylpiperazin-4-ylmethyl,
R⁴ is H,
m is 1,
n is 1
Y is O and
25 aryl in arylpiperazin-4-ylmethyl is phenyl
which is unsubstituted or substituted
once or twice by A, CN, OH, OA or Hal.

30 The method of the invention is particularly suitable
for synthesizing 2- or 3-substituted D4 receptor
ligands of the formula 5

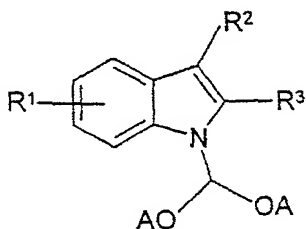


5

Elimination of the functionalized indole derivative after the synthetic chemistry has taken place on the solid phase takes place by acid hydrolysis, as known to the skilled worker, or by acid-catalyzed transacetalization. The functionalized indole derivative is preferably a mixture of 1,4-dioxane and hydrochloric acid in the ratio 1:1. Subsequent treatment with a base, preferably NaOH, liberates the free functionalized indole derivative. The acid-catalyzed transacetalization preferably takes place in the presence of an alcohol, in particular methanol or ethanol, and of a catalytic amount of p-toluenesulfonic acid, camphorsulfonic acid or in the presence of an acid ion exchanger.

The invention therefore likewise relates to a method for producing indole derivatives on a solid phase, characterized in that

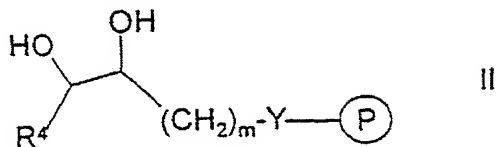
(1) dialkoxymethyl-protected indole derivatives of the formula I



in which

- 25 R¹ is H, A, Hal, OA, CF₃, OCF₃, CN, NA₂ or NO₂,
R² is H, A, -(CH₂)_o-Hal, OA, CF₃, OCF₃, CN, NO₂, COOA or Na₂,
R₃ is H, A, -(CH₂)_o-Hal, OA, CF₃, OCF₃, CN, NA₂, NO₂ or SnBu₃,
30 A is alkyl having 1 to 6 C atoms,
Bu is butyl and
o is 0, 1, 2 or 3,
with the condition that at least one substituent R¹, R² or R³ is not H,

is reacted with a solid phase II having vicinal diol groups



in which

(P) is a solid phase without terminal functional group,

10 R⁴ is H or A,

A is alkyl having 1 to 6 C atoms,

m is 1, 2, 3 or 4 and

Y is O, S, NH or NA,

(b) subsequent synthetic chemistry is carried out and

15 (c) the functionalized indole derivative is eliminated "without trace" from the solid phase by acid hydrolysis or acid-catalyzed transacetalization.

An efficient method for producing functionalized indole derivatives on a solid phase is thus made available. One advantage of this method is that indole derivatives which are already substituted by R¹ and/or R² and/or R³ can be bound to the solid phase for further functionalization in one synthetic step, it also being possible for the substituents R¹, R² and R³ to be sterically demanding and sensitive to hydrolysis (R³ = SnBu₃). A particular advantage is that indoles substituted by R¹ and/or R², where R¹ and/or R² is not H, i.e. indoles which are not substituted in the 3 position, can be bound to the solid phase for further functionalization. The solid phase-bound indole derivatives are moreover easy to obtain at reasonable cost.

Furthermore both the attachment and the elimination take place under slightly acidic conditions.

It is assumed that, even without further statements, a skilled worker will be able to make use of the above description in the widest scope. The preferred
5 embodiments are therefore to be regarded merely as descriptive, and by no means as in any way limiting disclosure.

The complete disclosure of all applications and
10 publications mentioned hereinbefore and hereinafter is incorporated in this application by reference.

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All temperatures stated hereinbefore and hereinafter are stated in °C. In the examples which follow, "usual working up" means: water is added if necessary, the pH is adjusted to values between 2 and 10 if necessary, depending on the constitution of the final product, extraction is carried out with ethyl acetate or dichloromethane and, after separation, the organic
15 phase is dried over sodium sulfate, evaporated and purified by chromatography on silica gel and/or by crystallization.
20

"Usual working up" means in the case of reactions on
25 the solid phase: the resin is filtered, washed alternately with methanol and dried under reduced pressure, preferably under 0.01 mbar, and at room temperature.

30 Example 1:

Synthesis of diethoxymethyl-protected indole derivatives

1 mmol of 1H-indole-5-carbonitrile is heated in 10 mmol
35 of triethyl orthoformate at a reaction temperature of 160° for 6 h. The usual working up results in 1-diethoxymethyl-1H-indole-5-carbonitrile, EI-MS: 244 (M⁺).

The result on analogous reaction of triethyl orthoformate

with 5-nitro-1H-indole is

1-diethoxymethyl-5-nitro-1H-indole, EI-MS: 264 (M^+);

5

with methyl 1H-indole-3-carboxylate is

methyl 1-diethoxymethyl-1H-indole-3-carboxylate, EI-MS: 277 (M^+);

with 2-chloromethyl-1H-indole-6-carbonitrile is

10 2-chloromethyl-1-diethoxymethyl-1H-indole-6-carbonitrile, EI-MS: 292 (M^+ , 35 Cl), 294 (M^+ , 37 Cl) and

with 2-chloromethyl-1H-indole-5-carbonitrile is

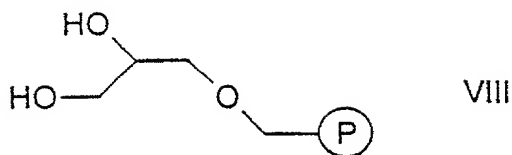
15 2-chloromethyl-1-diethoxymethyl-1H-indole-5-carbonitrile, EI-MS: 292 (M^+ , 35 Cl), 294 (M^+ , 37 Cl).

1 mmol of methyl 1-diethoxymethyl-1H-indole-3-carboxylate is dissolved in 20 ml of THF, and 1.2 mmol
20 of an n-butyllithium solution in n-hexane (1.6M) are added dropwise at -78° . The mixture is warmed to 0° and stirred for a further 30 min. 1.2 mmol of tributyltin chloride are added to this solution at -78° . A reaction time of 30 min is followed by pouring onto ice and the
25 usual working up. Methyl 1-diethoxymethyl-2-tributylstannanyl-1H-indole-3-carboxylate is obtained, EI-MS: 566 (M^+).

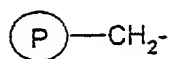
Example 2:

30 *Synthesis of the solid phase*

A suspension of 16 g of Merrifield resin (degree of substitution 1.08 mmol/g) and 4.1 g of sodium in 120 ml of 2,2-dimethyl-1,3-dioxolane-4-methanol is agitated at
35 room temperature for 20 h and then stirred at 80° for 24 h. After acid hydrolysis in 1,4-dioxane/HCl 1:1 and the usual working up for reactions on a solid phase, the dried resin of the formula VIII is obtained.



in which

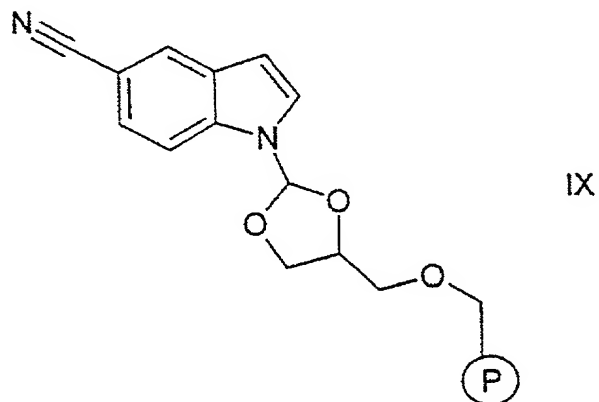


is Merrifield resin without the terminal functional group.

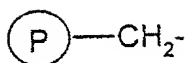
Example 3:

Transacetalization

A suspension of 1 g of the solid phase of the formula VIII in 10 ml of 1,4-dioxane and 100 mg of p-toluenesulfonic acid are stirred with 5 mmol of 1-diethoxymethyl-1H-indole-5-carbonitrile at room temperature for 3 h. The usual working up results in the solid phase-bound indole derivative of the formula IX



in which

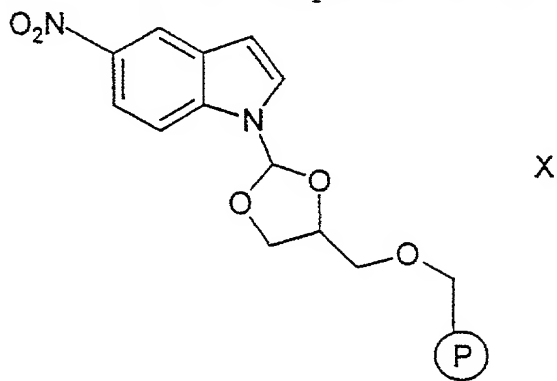


is Merrifield resin without the terminal functional group.

FTIR spectroscopy: $\nu = 2220 \text{ cm}^{-1}$ (CN).

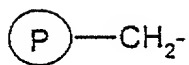
In analogy to Example 3, the solid phase of the formula VIII

- 5 is reacted with 1-diethoxymethyl-5-nitro-1H-indole. The result is the compound of the formula X



in which

10



is Merrifield resin without the terminal functional group;

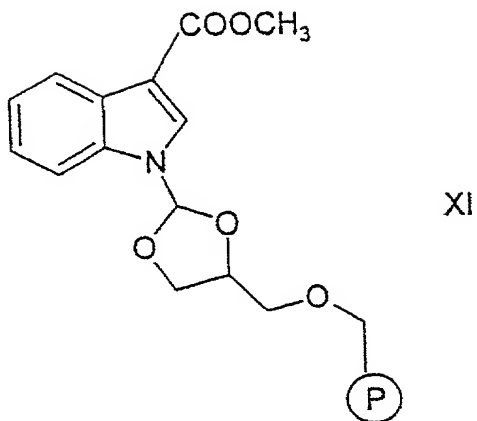
15

In analogy to Example 3, the solid phase of the formula VIII

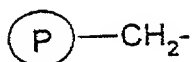
is reacted with methyl 1-diethoxymethyl-1H-indole-3-carboxylate. The result is the compound of the formula XI

20

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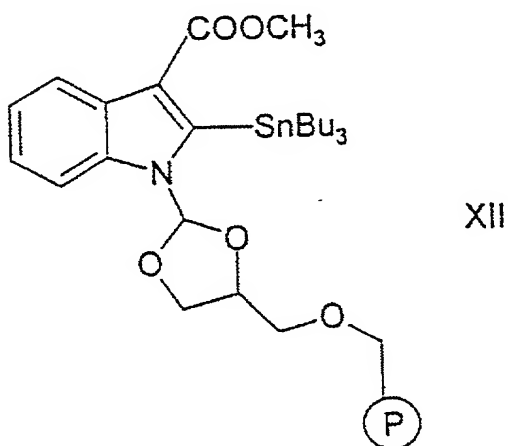
in which



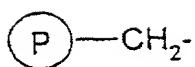
is Merrifield resin without the terminal functional group; FT-IR: $\nu = 1705 \text{ cm}^{-1}$ (CO);

In analogy to Example 3, the solid phase of the formula VIII

is reacted with methyl 1-diethoxymethyl-2-tributylstannanyl-1H-indole-3-carboxylate. The result is the compound of the formula XII



in which

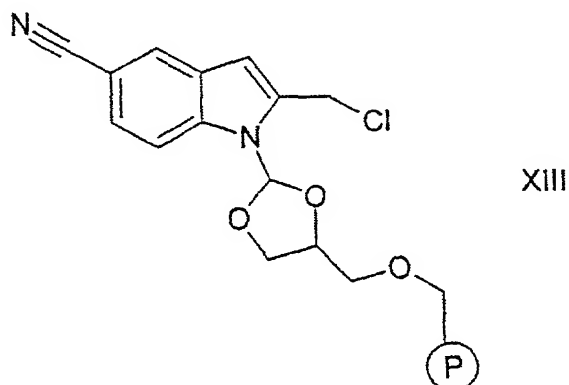


is Merrifield resin without the terminal functional group; FT-IR: $\nu = 1688 \text{ cm}^{-1}$ (CO);

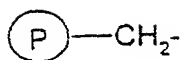
5 In analogy to Example 3, the solid phase of the formula VIII

is reacted with 2-chloromethyl-1-diethoxymethyl-1H-indole-5-carbonitrile. The result is the compound of the formula XIII

10



in which



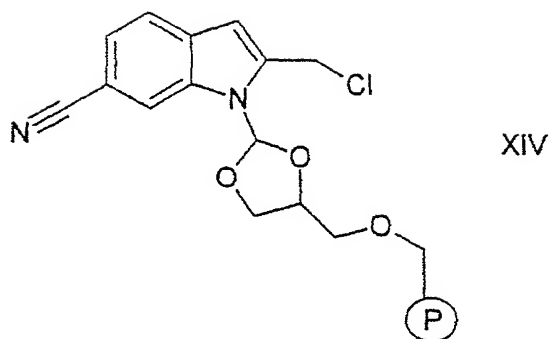
15 is Merrifield resin without the terminal functional group; FT-IR: $\nu = 2220 \text{ cm}^{-1}$ (CN) and

In analogy to Example 3, the solid phase of the formula VIII

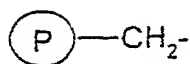
20

is reacted with 2-chloromethyl-1-diethoxymethyl-1H-indole-6-carbonitrile. The result is the compound of the formula XIV

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in which



is Merrifield resin without the terminal functional group; FT-IR: $\nu = 2220 \text{ cm}^{-1}$ (CN).

Example 4:

Elimination without synthetic chemistry

- 10 The compound of the formula IX synthesized in Example 3 is suspended in 10 ml of 1,4-dioxane/2N HCl (1:1) and heated at 40°. After 3 h, 2N NaOH is added dropwise at room temperature until the pH is 10 and, after stirring for a further 30 min, the solid phase is filtered off.
- 15 Pure precursor 1H-indole-5-carbonitrile is recovered. The loading is calculated as 0.72 mmol/g.

20 In analogy to the elimination of Example 4, the loading of the solid phase-bound compound of the formula X is calculated as 0.76 mmol/g.

In analogy to the elimination of Example 4, the loading of the solid phase-bound compound of the formula XI is calculated as 0.76 mmol/g.

25

In analogy to the elimination of Example 4, the loading of the solid phase-bound compound of the formula XII is calculated as 0.42 mmol/g. Under the elimination

conditions of Example 4 there is destannylation to give the eliminated product methyl 1H-indole-3-carboxylate.

Example 5:

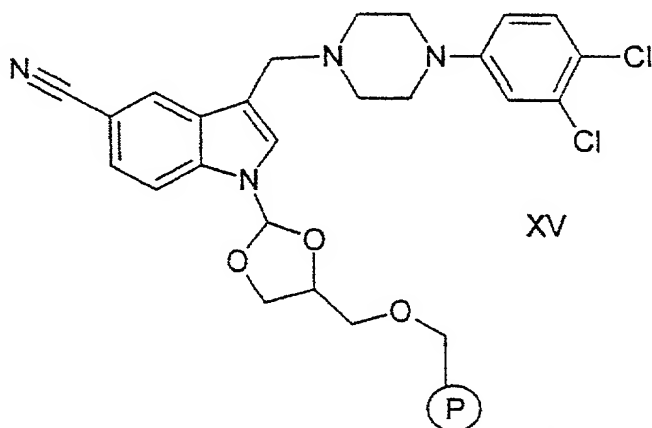
5 *Mannich reaction*

10 equivalents of dimethylmethyleimmonium chloride are added to a suspension of 1 g of the solid phase-bound compound of the formula IX in 10 ml of DMF at room temperature, and the mixture is stirred for 48 h. The usual working up is followed by elimination from the solid phase in analogy to Example 4. The result is 3-dimethylaminomethyl-1H-indole-5-carbonitrile with a yield of 99% and a purity of 98%, obtained by NMR analysis; EI-MS: 199 (M^+).

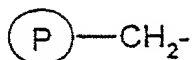
Example 6:

Mannich reaction

20 220 mg of the solid phase-bound compound of Example IX (prepared in Example 3) are suspended in 5 ml of glacial acetic acid/dichloromethane in the ratio 4:1, and 10 equivalents of 3,4-dichlorophenylpiperazine and 0.6 ml of formaldehyde solution (37% in water) are added. The mixture is stirred at 40° for 64 h. The usual working up results in the solid phase-bound functionalized indole derivative of the formula XV



in which



is Merrifield resin without the terminal
5 functional group.

The usual working up is followed by elimination from
the solid phase in analogy to Example 4. The result is
3-[4-(3,4-dichlorophenyl)piperazin-1-ylmethyl]-1H-
10 indole-5-carbonitrile.

The result on reaction of the indole derivative of the
formula IX in analogy to Example 6
15 with phenylpiperazine and acid hydrolysis is
3-(4-phenylpiperazin-1-ylmethyl)-1H-indole-5-
carbonitrile;

with 2-chlorophenylpiperazine and acid hydrolysis is
20 3-[4-(2-chlorophenyl)piperazin-1-ylmethyl]-1H-indole-
5-carbonitrile.

Example 7:

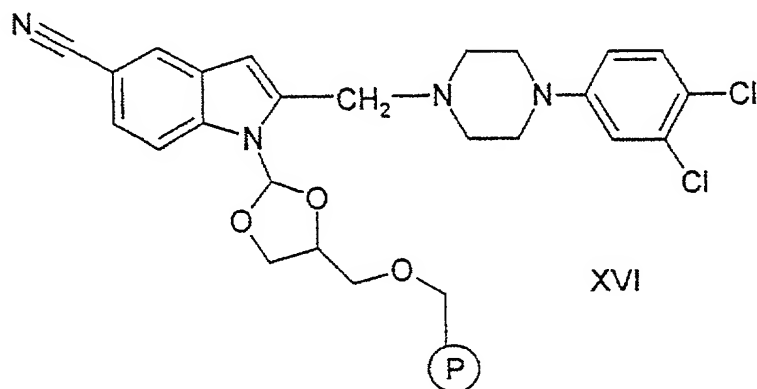
Stille coupling

25 114 mg of 4-bromobenzonitrile and 9 mg of Pd_2dba_3 , 19 mg
of $\text{tert-Bu}_3\text{P}$ and 45 mg of CsF are added to a suspension
of 150 mg of the solid phase-bound compound of the
formula XII in 10 ml of 1,4-dioxane, and the mixture is
30 heated at 100° for 48 h. The usual working up is
followed by elimination from the solid phase in analogy
to Example 4. The result is methyl 2-(4-cyanophenyl)-
1H-indole-3-carboxylate with a yield of 66%.

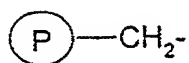
35 Example 8:

Nucleophilic substitution

160 mg of the solid phase-bound indole derivative of the formula XII are suspended in 5 ml of DMF, and 10 equivalents of 3,4-dichlorophenylpiperazine are added. The mixture is stirred at 40° for 48 h. The usual working up results in the functionalized derivative of the formula XVI



in which



is Merrifield resin without the terminal functional group.

The usual working up is followed by elimination from the solid phase in analogy to Example 4. The result is 2-[4-(3,4-dichlorophenyl)piperazin-1-ylmethyl]-1H-indole-5-carbonitrile. The loading of the solid phase of the formula XIII is calculated as 0.33 mmol/g for the reaction product.

20

The solid phase-bound indole derivative of the formula XIII is reacted in analogy to Example 8

with phenylpiperazine to result, after acid hydrolysis, in

25

2-(4-phenylpiperazin-1-ylmethyl)-1H-indole-5-carbonitrile;

with 2-chlorophenylpiperazine to result, after acid hydrolysis, in

2-[4-(2-chlorophenyl)piperazin-1-ylmethyl]-1-H-indole-5-carbonitrile.

5 The solid phase-bound indole derivative of the formula XIV is reacted in analogy to Example 8 with 3,4-dichlorophenylpiperazine to result, after acid hydrolysis, in 2-[4-(3,4-dichlorophenyl)piperazin-1-ylmethyl]-1H-indole-6-carbonitrile. The loading of the solid phase 10 of the formula XIV is calculated as 0.33 mmol/g for the reaction product.

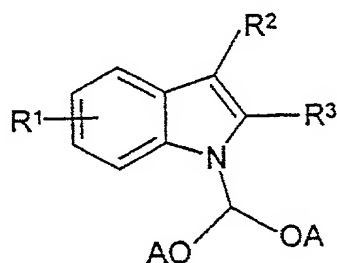
15 The solid phase-bound indole derivative of the formula XIV is reacted in analogy to Example 8 with phenylpiperazine to result, after acid hydrolysis, in 2-(4-phenylpiperazin-1-ylmethyl)-1H-indole-6-carbonitrile;

20 with 2-chlorophenylpiperazine to result, after acid hydrolysis, in 2-[4-(2-chlorophenyl)piperazin-1-ylmethyl]-1-H-indole-6-carbonitrile.

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Patent Claims

1. Method for producing indole derivatives on a solid phase, where the attachment to the solid phase takes place on the indole nitrogen through transacetalization of dialkoxymethyl-protected indoles with a solid phase which has vicinal diol groups and, after synthetic chemistry on the solid phase, the functionalized indole derivative is cleaved "without trace" off the solid phase.
2. Method according to Claim 1, where the attachment to the solid phase having vicinal diol groups takes place by transacetalization of dialkoxymethyl-protected indoles of the formula I



in which

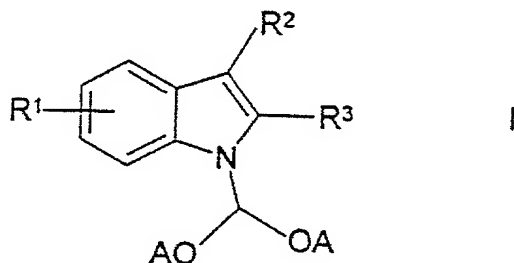
- 20 R^1 is H, A, Hal, OA, CF_3 , OCF_3 , CN, NA_2 or NO_2 ,
- R^2 is H, A, $-(CH_2)_o$ -Hal, OA, CF_3 , OCF_3 , CN, NO_2 , COOA or NA_2 ,
- R^3 is H, A, $-(CH_2)_o$ -Hal, OA, CF_3 , OCF_3 , CN, NA_2 , NO_2 or $SnBu_3$,
- 25 A is alkyl having 1 to 6 C atoms,
- Bu is butyl,
- o is 0, 1, 2 or 3
- with the condition that at least one substituent R^1 , R^2 or R^3 is not H.

30

3. Method according to Claims 1 and 2, where the synthetic chemistry is selected from the group of

nucleophilic substitution, Mannich reaction or Stille coupling.

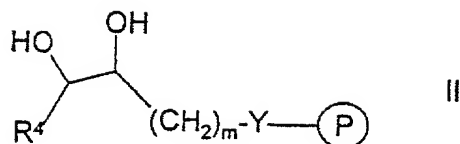
4. Method according to Claims 1 to 3, where the polymeric support material of the solid phase is selected from the group of crosslinked polystyrenes, crosslinked polyacrylamides or other resins, natural polymers or silica gels.
5. Method for producing indole derivatives on a solid phase, characterized in that
- (1) dialkoxymethyl-protected indole derivatives of the formula I



in which

- R^1 is H, A, Hal, OA, CF_3 , OCF_3 , CN, NA_2 or NO_2 ,
 R^2 is H, A, $-(CH_2)_o$ -Hal, OA, CF_3 , OCF_3 , CN, NO_2 ,
 $COOA$ or Na_2 ,
 R_3 is H, A, $-(CH_2)_o$ -Hal, OA, CF_3 , OCF_3 , CN, NA_2 ,
 NO_2 or $SnBu_3$,
A is alkyl having 1 to 6 C atoms,
Bu is butyl and
o is 0, 1, 2 or 3,
with the condition that at least one substituent R^1 , R^2 or R^3 is not H,

is reacted with a solid phase II having vicinal diol groups



in which

(P) is a solid phase without terminal functional group,

R⁴ is H or A,

A is alkyl having 1 to 6 C atoms,

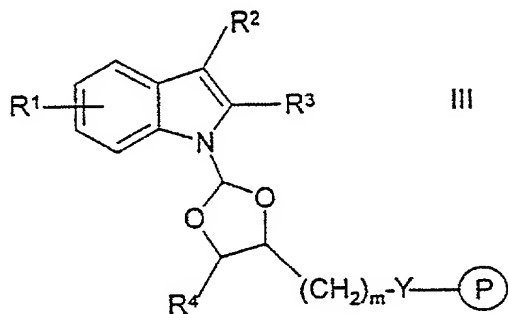
m is 1, 2, 3 or 4 and

Y is O, S, NH or NA,

(b) subsequent synthetic chemistry is carried out and

(c) the functionalized indole derivative is eliminated "without trace" from the solid phase by acid hydrolysis or acid-catalyzed transacetalization.

6. Compounds of the formula III



in which

(P) is a solid phase without terminal functional group,

R¹ is H, A, Hal, OA, CF₃, OCF₃, CN, NA₂ or NO₂,

R² is H, A, -(CH₂)_o-Hal, OA, CF₃, OCF₃, CN, NO₂, COOA -(CH₂)_n-NH₂, -(CH₂)_n-NHA, -(CH₂)_n-NA₂, Het or -(CH₂)_n-Het-Ar,

R³ is H, A, -(CH₂)_o-Hal, OA, CF₃, OCF₃, CN, NA₂, NO₂ Ar, Het, -(CH₂)_n-Het-Ar or SnBu₃,

R⁴ is H or A,

A is alkyl having 1 to 6 C atoms,

Ar is phenyl which is unsubstituted or substituted one, two or three times by A, CN, OH, OA or Hal,

Het is a mono- or binuclear saturated, unsaturated or aromatic heterocycle which has 1 to 4 N, O and/or S atoms and which may be unsubstituted or substituted one, two or three times by Hal, A, OH, OA, CF₃, CN or NO₂,

Bu is butyl,

n is 0, 1 or 2,

m is 1, 2, 3 or 4,

o is 0, 1, 2 or 3 and

Y is O, S, NH or NA,

with the condition that at least one substituent R¹, R² or R³ is not H.

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Zur Erklärung der Zweibuchstaben-Codes, und der anderen
Abkürzungen wird auf die Erklärungen ("Guidance Notes on
Codes and Abbreviations") am Anfang jeder regulären Ausgabe
der PCT-Gazette verwiesen.

(54) Title: METHOD FOR PRODUCING INDOLE DERIVATIVES ON A SOLID PHASE

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON INDOLDERIVATEN AN FESTER PHASE

(57) Abstract: The invention relates to a method for producing indole derivatives on a solid phase. Binding to the solid phase is carried out on indole nitrogen by means of a transacetalisation of dialkoxymethyl-protected indoles with a solid phase that carries vicinal diol groups. After synthetic chemistry on the solid phase, the functionalised indole derivative is separated from the solid phase in a traceless manner.

(57) Zusammenfassung: Die Erfindung betrifft ein Verfahren zur Herstellung von Indol-Derivaten an fester Phase, wobei die Anbindung an die feste Phase am Indol-Stickstoff durch Transacetalisierung von dialkoxymethylgeschützten Indolen mit einer festen Phase erfolgt, die vicinale Diolgruppen trägt und nach Synthesechemie an der festen Phase, das funktionalisierte Indol-Derivat "spurlos" von der festen Phase gespalten wird.

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